THE MIGRAINE ATTACK: PATHOPHYSIOLOGY AND GENETICS

By

Ann M. Weber

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To the faculty of Washington State University:

The Members of the committee appointed to examine the project of Ann M. Weber find it satisfactory and recommend that it be accepted.

Chair: Billie Severtsen, Ph.D., R.N.

Lorna Schumann, Ph.D., NP-C, CCRN, FNP, ACNP, FAANP

Anne Hirsch, Ph.D., ARNP-BC, FNP
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Abstract

By Ann M. Weber

Washington State University
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Chair: Billie Steversen

Despite a decade of progress, migraine headache remains prevalent, disabling, often undiagnosed, and undertreated. Migraines affect approximately 24% of the population, with 6% being men and approximately 18% being women. Analgesic overuse, insomnia, depression, and anxiety are often comorbid with migraine headaches, leading to an annual cost of labor lost and disability of $50 billion. Research has demonstrated a connection between genetic influence with neuronal and vascular imbalances in the central nervous system, leading to the emergence of the condition. This new knowledge, may one day, help in treating this chronic condition. Current treatment options include abortive and preventative therapies. The goal of therapy is to reduce frequency and severity of attacks, limiting the impact of migraine on activities-of-daily living.
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Introduction

Despite a decade of progress, migraine headache remains prevalent, disabling, often under diagnosed, and undertreated. Migraines affect approximately 24% of the U.S. population, with 6% being men and approximately 18% being women (Mathew, 2001). Analgesic overuse, insomnia, depression, and anxiety often comorbid with migraine headaches, leading to an annual cost of labor lost and disability of $50 billion (Mathew, 2001).

Individuals who suffer from migraine headaches characterize their condition in relationship to how it affects their lives, their incentive to seek medical attention, and the condition itself. Thirty-five percent of patients believe that migraine headache influences social plans, 40% admit being worried about the possible occurrence of headache at a future event, and approximately 45% worry about driving because of a headache. Sixty-one percent of migraine sufferers felt that their condition impacted their family life (Olesen, Tfelt-Hansen & Welch, 1999).

It is important for the primary care provider to understand and recognize that migraine is more than a headache, it is a whole-body syndrome that causes debilitating pain. Migraine sufferers pose challenges to the primary care provider because of their complexity and variability. Migraines include systemic symptoms of nausea, photophobia and phonophobia. This type of headache can have a devastating impact on quality-of-life and activities-of-daily living, perhaps to a greater degree than any other chronic condition (Fox, 2002). These qualities pose an exceptional treatment challenge for clinicians (Fox, 2002). Of the estimated 14 million patients who should be receiving some form of medication for migraines, only 3.5 million actually get them. It has been estimated that approximately five million migraine patients experience disabling pain at least three days per month. A portion of the problem of under
diagnosis lies with health care professionals, who are not asking patients the right questions about their headache complaints and therefore are often missing the precise diagnosis (Beyzarov, 2000). The other half of the problem lies with the patients. Most consumers attribute migraine headaches to sinusitis, stress or lack of sleep. Many times, patients self-treat with over-the-counter medications, excluding themselves from professional diagnosis and treatment, including prescription therapies thus making this self-treatment cycle one of the biggest obstacles to receiving appropriate care (Beyzarov, 2000).

Migraine is probably linked to disordered regulation of brain neurotransmitters, most prominently the serotonergic system (Fox, 2002). Advances in molecular biology, coupled with noninvasive imaging studies, have allowed researchers to see actual changes in the brain that occur during migraine attack. The findings that have arisen from these observations have resulted in numerous breakthroughs in the management of migraines (Beyzarov, 2000). These include abortive therapies such as the use of triptans and preventative therapy including beta blockers. Such therapies often relieve pain from this chronic and often disabling condition. Along with these treatment modalities, continuing research in molecular biology and genetics will offer future and more effective treatments for migraine sufferers.

**Classification of Migraines**

Migraines are classified based on patient presentation. The diagnosis is based on patient history and clinical presentation. Migraines are defined into two areas, migraine with aura (MWA) and migraine without aura (MWOA) (Mathew, 2001). Migraine with aura is characterized by a number of symptoms that a client experiences before the actual onset of migraine pain. The aura will occur approximately 20 minutes before onset of pain and last no longer than 60 minutes (Olesen et al., 1999). The aura may consist of both visual and auditory
stimulus that represent the onset of a migraine attack. These symptoms can be defined as abnormalities in both the visual and auditory sensory areas that signal the onset of a migraine. Clinically, the visual aura consists of both positive symptoms, in the form of a scotoma, an island-like blind gap in the visual field. Small multiple scotomas or a single, dense scotoma may be present (Khalil, Legg & Anderson, 2000). The visual aura, which is the most common form of migraine aura, spreads laterally in one hemifield, accelerating and enlarging as it spreads (Mathew, 2001).

Auditory aura may consist of a number of characteristics from abnormal noises to an increase in sensitivity to certain amplitudes in wave frequencies (Olesen et al., 1999). These types of auras can cause nausea, sensitivity to sound or changes in auditory perception (Mathew, 2001). Other auras can include unilateral weakness of the extremities or speech difficulty. The criteria for diagnosis of migraine with aura includes one or more reversible aura symptoms, with at least one aura that develops over four minutes and does not last longer than one hour and precedes the onset of headache pain (Olesen et al., 1999).

Migraine without aura is the most common form of migraine (Olesen et al., 1999). The diagnostic criteria for migraine without aura is listed in Table 1 by the International Headache Society (HIS). These individuals do not experience auras and typically the onset of migraine attacks present with the onset of pain and an associated symptom such as, nausea/vomiting and photophobia/phonophobia. These symptoms are not auras because they occur simultaneously with the onset of pain. Typically, the pain lasts between 4 hours and up to 72 hours, with unilateral location. The pain is usually defined as pulsating with a moderate to severe intensity, with increased symptoms with activity. During the migraine, at least one associated symptom of
nausea/vomiting or photophobia/phonophobia must be present for the headache to be classified as a migraine according to International Headache Society guidelines (Olesen et al., 1999).

**Pathophysiology**

Migraine attacks are known to involve alterations in the regulation of vascular and neuronal systems (Olesen et al., 1999). Other areas of research include hypothalamic involvement and the regulation of neurochemicals (Perez, Sanchoz, Seabra & Tufik, 2001). The threshold for migraine may be genetically determined. Channelopathy, one of the genetic theories associated with migraines, is the concept of neurophysiologic influence on vessels and neurotransmitters within the brain (Peres et al., 2001). Recent research has demonstrated that the link between genetic and neurovascular pathways may contribute to both initial attacks and subsequent chronic migraine pain (Peres et al., 2001). At the core of research is the theory that calcium channels may be directly responsible for both vascular and neurological chaos during a migraine attack (Mathew, 2000). Calcium channels are found throughout the body directly regulating the influx of calcium within the cell and helping in certain areas of the body, especially the myocardium, to prolong action potentials. Leakage in similar calcium channels are known to influence such conditions as myocardial infarcts and arrhythmias (Mathew, 2000). Researchers have also examined sub-sets of these channels in migraine attacks (Ophoff, Terwindt, and Vergouwe, 1996). A specific type of calcium channel has been identified as a potential cause for the severe pain and systemic affects that migraines produce. The P/Q-type calcium channel alpha 1a subunit which lies on chromosome 19p13 is a specific type of calcium channel that has been implicated in migraine attacks (Ophoff et al., 1996). Possible variations and mutations along this channel may cause what is known as a channelopathy or imbalance in calcium regulation by the channel. Additionally, P/Q-type calcium channelopathies, responsible
for nerve stimulation and neuromuscular transmission, show mild abnormalities related to migraine with prolonged aura (Sandor, Macia & De Pasqua, 1998). This abnormal functioning of calcium ion channels leads to abnormalities in nerve transmission and neurotransmitter communication. Imbalances in neurotransmitters are believed to cause wide spectrum changes in brain vessels including neuronal hyperexcitability and trigeminal vascular constriction. These changes further aggravate the neuronal system causing additional channelopathy (Mathew, 2001).

The vascular component of migraine attacks is known to involve alterations in the regulation of vascular tone in intra and/or extra-cranial blood vessels. The nature of these alterations is not clearly established although a number of factors have been studied. Among these are neurotransmitters, ligands, signaling molecules and paracrine molecules. These chemical substances originate from the sympathetic, parasympathetic and sensory neuronal areas. Other possible causal agents include endothelial, mast and white blood cells. Some chemicals such as nitric oxide, prostaglandin I\textsubscript{2} and endothelium-derived hyperpolarizing factor, regulate tone and relaxation of cranial blood vessels have been analyzed. (Olesen et al., 1999). Other areas of research to determine the etiology of migraine, include hypothalamic involvement with the subsequent regulation and nocturnal secretion of melatonin, prolactin, growth hormone and cortisol (Peres, Rio, Seabra & Tufik, 2001). Alterations in any, some or all of these chemicals may be linked to brain vessel constriction leading to migraine pain (Peres et al., 2001). It is believed that imbalances in nerve communication, through channelopathy, and disruption of the vascular bed tone leads to migraine attacks and systemic symptoms (Peres et al., 2001). This ongoing research may one day lead to advancements in treatment for this debilitating condition.
Neuronal and Vascular Responses

Abnormalities and imbalances in neurotransmitters caused by channelopathy are believed to cause wide spectrum changes in brain vessels. When activation of either the cerebral cortex or the brainstem occurs, due to external stimuli or triggers, activation of the trigeminal vasculature occurs leading directly to migraine pain (Mathew, 2001). This occurs because of trigeminal involvement in ophthalmological and auditory functioning regions, disrupting both neuronal and vascular balance around the frontal portion of the head (Olesen et al., 1999). Trigeminal activation in this situation causes cyclical aggravation and imbalance of the vasculature and neuronal beds in the area resulting in increasing, pulsating pain that is typical for a migraine. In addition, the trigeminal nerve’s anterior portion of the spinal nerves C2 and the posterior portion of C3 carry pain sensation, of the head, face and upper neck to the cerebral cortex and brainstem. A practical application of this neuronal circuit are the triggers of neck muscle tenderness, neck pain, and spasms which account for 75% of initial migraine pain (Kanecki & Totten, 2001).

The trigeminal nerve innervates the dural and pial blood vessels, the dural sinuses and the dura mater. The intracranial blood vessel receptors are richly supplied by trigeminal, sympathetic and parasympathetic nerve endings. Blood vessels containing post-synaptic 5-HT1B receptors are located in these areas and been identified as areas that can be targeted for pain relief with the use of 5-HT1b blockers or triptans (Kaniecki & Totten, 2001).

Two changes occur due to the activation and sensitization of the trigeminal vascular system. First, vasodilation of dural blood vessels and second, subsequent neurogenic inflammatory reactions. Dilation of blood vessels causes abnormal release of neurochemicals, stimulating nerve endings, releasing neuropeptides, a substance known as substance P, histamine, vasoactive substances and neurokinin A. These vasoactive peptides cause further blood vessel dilation and lead to a rapid-onset, inflammatory reaction and changes in the
perivascular area (Kaniecki & Totten, 2001). These changes result in dilation, swollen and inflamed blood vessels, and activation of pain receptors at the trigeminal nerve endings. The pain sensation is carried through the trigeminal nerve, (First-order neuron), into the second-order neurons in the brainstem resulting in the throbbing head pain that is aggravated by pulsations of the arteries. Activities that increase intracranial pressure, including physical exercise, bending down, coughing and sneezing, aggravate the pain in migraine. Further sensitization can lead to vertigo, nausea and/or vomiting. This sensitization of the first-order neuron explains why migraine sufferers prefer to stay quiet and not move during an attack. Additionally, chronic sensitization of the central nervous system, as just described, can cause permanent changes in vascular and nociceptive centers in the brain, accounting for daily headaches with repeated attacks (Mathew, 2001).

**Triggers and Etiologies**

The triggers of migraine attacks can be divided much like the categories and types of migraine headaches that exist. Triggers include anything that may precipitate an attack for a MWA (Migraine With Aura) and a MWOA (Migraine Without Aura). These include certain foods, stress, sleep imbalances, exercise, hormones and many others. A standard etiology does not exist for all migraines. The etiology behind the different types of migraine are specific to the classification of migraine a patient experiences. Migraines with aura differ in the pathophysiology and etiology from those of MWOA (Mathew, 2001).

Research including neuroimagining studies, clinical observation and blood flow measurements clearly indicate that migraine with aura originates from the cerebral cortex (Mathew, 2001). However, findings from functional PET scans (Positron Emission Tomography) of patients with MWOA have shown activation of the brainstem during an attack.
Migraine without aura differ from those with aura because of the specific activation of the brainstem, leading to activation of the trigeminal nerve causing neuronally mediated vascular changes (Bahra, Matharu, Buchel, Frackowiak & Goadsby, 2001). Please see Figure 1 and 2 for complete pathophysiology of MWA and MWOA.

**Genetics**

The genetic theory of channelopathy has been suggested as one of the possible causes of migraine attacks and subsequent pain. Magnetic resonance images (MRI), positron emission tomography (PET), and electrograms are helping to map the progression of a migraine through the central nervous system, aiding in the clinical determination of migraine headache (Mathew, 2001). Recent neurophysiological studies found that P/Q-type calcium channelopathies, responsible for nerve stimulation and neuromuscular transmission, showed mild abnormalities related to migraine with prolong aura (Sandor, Macia & De Pasqua, 1998).

Genetic epidemiology has shown that the risk to first-degree relatives with migraine with aura is 4-fold, whereas with migraines without aura is 1.9-fold (Russell & Olesen, 1995). Genetic studies in familial hemiplegic migraine (FHM), are similar to this finding. FHM, a rare autosomally inherited subtype of migraine with aura, has increased the potential of revealing other specific genetic defects associated with migraine headaches. Clinical manifestations of individuals with FHM include, hemiplegia outlasting the headache, coma, cognitive impairment, cerebellar ataxia, retinal degeneration and deafness. Individuals with this condition, may have migraine with neurological manifestations, while others will experience ordinary migraine with or without aura (Haan, Terwindt & Bos, 1994). Clinical observations suggest that FHM is part of a migraine spectrum with gene association, including both MWA
and MWOA suggesting that eventually genes specifically linked to migraine may be identified (Ophoff, Van Eijk & Sandquijl, 1994).

One study found that in one half of families with FHM the responsible gene deficit matched to chromosome 19p13 (Joutel, Bousser & Biousse, 1993). Munchau, Vahente, Shahidi and Eunson (2000) found that of the members they examined with the 19p13 gene deficit, 30% were definitively affected by FHM. In addition, they found that transmission patterns followed an autosomal dominant pattern with reduced penetration occurrence.

Ophoff, Terwindt, and Vergouwe (1996) further demonstrated that mutations on chromosome 19p13 occur more specifically in the P/Q-type calcium channel alpha 1a subunit in gene (CACNA1A). Munchau et al., (2000) suggested that such abnormalities in ion channels may be due to mutations in other genes, as well. Sibling-pair analysis, performed in affected siblings in families with migraine, with and without aura, demonstrated shared marker alleles of locus B195394, which is directly linked to CACNA1A (May, Ophoff & Terwindt, 1995). This suggests that family members with the same allele markers, exhibit migraine headaches due to mutations in gene expression. Recent neurophysiological studies found that P/Q-type calcium channelopathies showed mild abnormalities related to migraine with prolonged aura (Sandor, Macia & De Pasqua, 1998).

Recent research has reported an association between angiotensin-converting enzyme (ACE)-D allele with a specific type of migraine. Reports suggest an association between migraine without aura and ACE-D allele polymorphism. Paterna et al., (2000) examined 302 patients with diagnosed migraines without aura, based on diagnostic criteria from the International Headache Society Guidelines, with no history of cardiovascular diseases. They found that 48.34% of the patients who suffer from migraine without aura showed a higher
incidence of the ACE-D gene. In addition, plasma ACE activity was increased in patients with the ACE-D gene associated with an increased incidence of migraine attack. If the basic abnormalities of migraine are genetic and the genetic influence on neurochemicals, new technologies and medications may be developed including possible P/Q-type calcium channel regulators, specific ACE inhibitors or medications associated with inhibiting “central neuronal hyperexcitability” (Mathew, 2001).

Migraine With Aura

Migraine associated auras are connected to channelopathies that may produce alterations in signal-to-noise processing. This is the connection made in the central nervous system between auditory and ophthalmological input and the brain’s ability to process and balance both sensory stimuli and input. This failure to balance these aspects of input may cause a migraineur, (an individual who suffers from migraine), to be extraordinarily sensitive to ordinary sensory stimuli. Research has found that migraine sufferers demonstrate a potentiation of visual event-related potential (ERPs), auditory ERPs, and interictal potentiation of passive auditory ERPs or the periods between signals (Schoenen, Wang, Albert & Delwaide, 1995).

Kahalil, Legg, and Anderson (2000), investigated visual functioning in migraine using visual evoked potentials (VEP). These researchers discovered large amplitude waves both during and between migraine attacks. They considered them to be spontaneous neuronal discharges, with a turnover of high energy phosphates. Over the visual cortex this can produce illusions of light, (phosphenes), and over the motor cortex it can elicit motor evoked potentials (MEPs), which may be responsible for the visual and auditory auras experience. These researchers, along with a number of pharamaceutical companies, have investigated drugs that are specifically designed to treat migraine auras, specifically visual and auditory. They also are
investigating how treating these auras may decrease or abort the onset of migraine pain, nausea and/or vomiting, photophobia and phonophobia (Mathew, 2001).

Cao, Welch, Aurora, and Vikingstad (1999) further investigated visual auras. The term, spreading depression of Leo, is used to describe a neuroelectric event beginning in the occipital cortex and propagating into contiguous brain regions. This neuroelectric event is associated with a transient, but pronounced cerebral blood flow increase that precedes hypoprofusion. Researchers presume that this increased neuronal blood flow is due to the increased substrate demand of neurons attempting to repolarize. Overlaying transition color maps on anatomical images of people who suffered from migraine with aura, were examined to identify similarities and differences (Cao et al., 1999). The results demonstrated that the movement of decline of hypoprofusion as it progressed from the initiating area into contiguous cortical areas was not a random pattern of suppression but rather, was followed by recovery of profusion. Patients with triggered headache and visual change had statistically significant increases (p<0.001) in initial intensity of blood flow prior to the onset of migraine or visual change. The increase in this intensity was associated with decreased visual activation and thus, suppression of activation tied directly to vasodilation and hyperoxia. The decreases in visual activation may also reflect increased oxygen consumption by the neurons responsible for visual stimuli in the region. This in turn causes relatively decreased oxygenation of the tissue. In addition, the initial stage of induction of a migraine is connected to nitric oxide and calcitonin generated peptitides, released during the vasodilation phase (Cao et al., 1999). Researchers postulate that this may be mediated by the trigeminal nerve, which would account for migraine pain (Cao et al., 1999).

Khalil et al., (2000) examined long-term progression of VEPs in those individuals who suffered from migraine with aura for longer than 10 years and up to 20 years. They found
reduction in VEPs in chronic migraine was associated with visual cortex ischemia. Blood flow dropped by 50-60% in these areas during an attack. This degree of ischemia may lead to deficits, if damage is repetitive. The cell damage caused by ischemia produces a neurotoxic effect from the action of excitatory amino acids, which can cause neuronal damage. Cell loss in ischemia causes impaired cell function and further extends damaged neurotransmission, thus, extending on imbalance in neurochemicals and determining the degree of chronic migraine with aura (Cao et al., 1999).

**Migraine Without Aura**

Migraine without aura differs slightly in the channelopathy than that of migraine with aura. This type of migraine is triggered in the rostral brainstem, instead of the cerebral cortex, ultimately causing activation of the thalamus and, subsequently the neurotransmitters and hormones. Imbalances and hyperexcitability of these brain chemicals cause migraine pain, vascular hypoperfusion and chronic neuronal dysfunction. Using PET scanning (Positron Emission Tomography), activation of the rostral brainstem can be seen. Three distinct regions of the brain are activated during the migraine attack without aura, compared with that of the resting state. First, activation of the rostral brainstem is noted. Second, bilateral activation of the structures outside the brain corresponding to the region of the intracranial and extracranial blood vessels are observed. Third, there is activation of the anterior and posterior cingulated cortices, the prefrontal, posterior insular, and cerebellar cortices, bilaterally. This leads to the activation of the left thalamus, superior parietal cortex, the supplementary motor cortex and the lentiform nucleus. Ultimately, this leads to the activation of the trigeminal nerve. Once pain relief is achieved activation in these areas is still observed, suggesting that the activation of these areas is not only a response to a migraine attack and subsequent pain, but also trigeminal nerve
medication of the vasculature (Bahra, Matharu, Buchel, Frackowiak & Goadsby, 2001). Night and Goadsby (1999) found that the amount of periaqueductal gray matter (PAG), reduces nociceptive input in the brainstem. However, when stimulation of the trigeminal nerve occurs, in migraineurs, PAG does not function correctly. This syndrome leads to propagation of the vascular changes in the brainstem and subsequent attacks and migraine pain.

**Hypothalamus**

Migraine headaches have also been associated with hypothalamic dysfunction. Perez, Sanchez del Rio, Seabra and Tufik (2001) examined hypothalamic involvement in migraine headaches. The researchers found that there was a decreased prolactin peak secretion, increased cortisol concentration, a phase delay in the melatonin peak, and lower overall levels of melatonin in people who suffer from migraine. In this study, 47% of patients who suffered from chronic migraines had a significant phase delay in the melatonin peak and suffered insomnia due to this delay. When treated with 5 mg of melatonin there was a greater improvement in both sleep and migraines. Statistically, p<0.05 and significantly lower rates of 51.9%, of insomnia and migraine was found in these patients (Peres et al., 2001).

The circadian rhythm of melatonin secretion is regulated by the suprachiasmatic nucleus in the hypothalamus. Melatonin is a potent endogenous scavenger of reactive oxygen species acting as a neuroprotective agent in processes involving free radical formation and excitatory amino acid release (Perez et al., 2001). It is hypothesized that dysfunction in melatonin secretion may contribute to sensitization and persistence of inflammatory products causing vascular imbalance and increased frequency of migraine attacks (Perez et al., 2001).

Fox and Davis (1998) showed a diurnal variation in migraine onset related to decreased melatonin and abnormal levels of other diurnal hormones. Of 3,582 migraine attacks in almost
1,700 patients, the peak onset of migraine was in the early morning period between 5 am and 6 am. Melatonin may at some point play a role in management of migraines, because it may potentiate gamma-aminobutyric acid (GABA) inhibitory effects and inhibits prostaglandin E synthesis. Fox and Davis (1998) also identified GABA, an inhibitory presynaptic neurotransmitter, regulates muscle spasms, preventing uncontrolled muscle spasms, which may account for some migraine pain. Prostaglandin E has been identified as a substance that enhances receptor response to noxious stimuli, in other words it increases the body’s awareness and ability to feel pain (Perez et al., 2001).

Perez et al., (2001), found a decreased nocturnal prolactin peak in individuals with migraine. It is postulated that abnormalities in the anterior pituitary are linked to this decreased peak and hypersensitivity to certain neurotransmitters. Many migraineurs manifest hypersensitivity of dopamine receptors; yawning, nausea, vomiting, and hypotension in response to dopaminergic agonists. The hypersensitivity also causes increased tumor necrosis factor-alpha, a potent proinflammatory cytokine, involved in pain and inflammation that has been shown to inhibit prolactin release. Researchers hypothesize that the suppressive peak of prolactin leads to neurogenic inflammation and an increase in tumor necrosis factor-alpha (TNF) (Perez et al., 2001).

In addition to prolactin suppression, dopamine hypersensitivity and neuronal up-regulation inhibits growth hormone secretion. Inhibition of growth hormone leads to deregulation of neuropeptides, neurotransmitters, and opiates, all associated with nociceptive activity (Perez et al., 2001).

Cortisol concentrations are raised in many conditions related to chronic migraines; depression, anxiety, insomnia, fibromyalgia, and chronic pain. Higher concentrations of cortisol
were found in those individuals with chronic migraine (CM). Glucocorticoids exert numerous effects on metabolism, inflammation and immunity. Long-term effects of hypercortisolism leads to arterial hypertension and may be responsible for the transformation from episodic to chronic daily headaches. The increase in cortisol concentrations may be the biological basis for the vascular component of chronic migraine attacks by causing persistent vasoconstriction (Perez et al., 2001).

**Phases of Migraine Attack**

The migraine episode can be divided into five distinct phases: (a) premonitory symptoms, (b) aura, (c) headache pain and associated symptoms, (d) resolution, and (e) recovery (Table 3). In migraine, headache is an essential part of the diagnosis. Although the headache pain may not be preceded by any identifiable focal symptoms of neurologic disturbance, it may be preceded by premonitory symptoms. These can be quite characteristic for the individual patient and clearly identifiable as warning symptoms of an impending attack (Olesen et al., 1999).

**Premonitory Symptoms**

The headache classification committee, a committee made up of experts in headaches, neurology and headache treatment, states that in migraine attacks, premonitory symptoms can precede the attack by hours or up to one to two days (Olesen et al., 1999). These symptoms are classified as excitatory or inhibitory. Excitatory premonitory symptoms include irritability, physical hyperactivity, increased sensitivity to light and sound, food cravings, and thirst. Inhibitory symptoms include mental withdrawal, behavioral sluggishness, feeling tired, difficulty focusing, poor concentration, yawning, and anorexia (Olesen et al., 1999).
Precipitating Factors

Precipitants are common migraine trigger mechanisms, (Table 2), that alone, or in combination with other environmental exposures, induce headache attacks in susceptible individuals. Precipitants cannot be considered universal because the presence of a factor does not always trigger an attack in the same individual (Olesen et al., 1999).

One or more precipitating factors have been described in 64% to 90% of patients with migraine. Overall, they are more common in patients with migraine without aura, than those with aura. Up to 62% of female sufferers report menstruation as a common precipitating factor. Between 20-50% of patients report alcohol consumption as a precipitating factor and 45% of migraine sufferers report chocolate, dairy foods, citrus fruit, and fried fatty food as being common precipitating agents. Others report stress, mental tension, fatigue, and weather changes as precipitating agents. Oversleeping and undersleeping have also been cited as triggers (Olesen et al., 1999). These findings suggest multifactorial trigger mechanisms for individual attacks.

The Attack

In many instances, the initial phase of the headache pain cannot be localized to any particular part of the head. In addition, the aura can mask symptoms of initial onset of the attack. The aura is described as the beginning phase of the attack for those who suffer from MWA. The pain progresses over a period of one-half to two hours or more from a mild ache to a pain of moderate or marked severity. It is usually localized to one side of the head and is throbbing in nature. Associated symptoms including nausea, vomiting, diarrhea, photophobia, and phonophobia usually follow. The pulsating nature of the headache can be aggravated by routine physical activity and activities-of-daily-living (Olesen et al., 1999).
Resolution of the Attack

In most patients the headache resolves slowly by fading away; this can take from 24 to 72 hours. A minority of sufferers discover that sleeping for a few hours will abolish the headache, whereas others find that vomiting will arrest an attack (Olesen et al., 1999). After resolution of an attack many patients do not feel entirely back to normal, they often remain symptomatic for up to a day. Many report changes in mood, muscular weakness, physical tiredness and reduced appetite (Olesen et al., 1999).

Differential Diagnosis

Primary headaches, with no other associated disease present, involve vascular changes, pressure, muscle spasm and inflammation. Secondary headaches are attributed to organic diseases, such as tumors or meningitis and account for 2-10% of headaches. Choices of diagnostic tests are determined by history, physical and clinical presentation. A clinician must consider the age, gender, family history, onset and development of the headache in the initial evaluation (Edmeads, 1998). Please see Table 4 for outline of differential diagnoses.

Differential diagnosis must always include attention to potentially life-threatening conditions. A clinician must always be aware of embolic or hemorrhagic cerebrovascular accidents (CVAs), intracranial abscesses, meningitis and arteriovenous malformation (AVM) (Jackson, 1998). One must consider psychological condition, level of consciousness, signs of nuchal rigidity, pupillary changes or other focal neurological signs that may indicate the need for Computed Tomography (CT). A clinician must determine, if the headache is due to trauma or subsequent injury (Edmeads, 1998). Table 4 lists differential diagnoses for migraine and figure 3 details an algorithm for migraine diagnosis.
**Meningitis**

Viral and bacterial meningitis, along with cerebral abscesses, cause severe headaches that are usually followed by fever and malaise. Symptoms include nuchal rigidity, photophobia, fatigue and vomiting. Diagnostic tests usually include a lumbar puncture with gram staining, white blood cell count and culture of cerebral spinal fluid, and a complete blood count with white blood cell differential. To confirm the diagnosis a CT scan may be indicated, if focal neurological changes develop (Olesen et al., 1999)

**Cerebral Vascular Accidents and Tumors**

Focal or more pronounced system-wide neurological changes can accompany a CVA (Cerebral Vascular Accident) or AVM (Ateriovenous Malformation). A patient may complain about a headache that is followed by motor, sensory, or cognitive deficits due to cerebral ischemia. Hemiparesis, inability to swallow, aphasia, loss of consciousness or decreased LOC are indications for immediate CT scan (Olesen et al., 1999).

Many patients with an intracranial tumor report a headache of recent onset, that becomes more severe and frequent, and causes awakenings in the night or early morning. Many patients begin to notice deficits, depending on the location of the tumor, that become more pronounced over time. In these cases where there is a possibility of an intracranial tumor, a CT scan should be completed with appropriate follow-up with a neurosurgeon (Olesen et al., 1999).

**Temporal Arteritis**

Temporal arteritis and sinusitis can produce severe facial pain that can spread to the frontal and temporal areas of the head. With temporal arteritis there is usually a palpable mass along the side of the face that is warm to touch and is erythematous. Patients complain of pulsations along the side of the face with visual changes. A sedimentation rate should be drawn
in this case and referral to either an ophthalmologist or neurologist should be made immediately. In those individuals with sinusitis, a clinician should determine, if this is a new onset problem or a chronic condition. If the problem has persisted over a length of time and has not resolved with antibiotics and other treatments a CT scan should be completed to investigate sinus malformations (Olesen et al., 1999).

**Hypertension**

Hypertension headaches should be considered in the differential. Hypertension headaches are usually associated with elevated blood pressure readings and are alleviated when the blood pressure is reduced. Many patients find that they can “tell” when their blood pressure is elevated by the degree of the headache (Cunningham, 1999). Adequate control of the blood pressure, with diet, exercise and medication can alleviate these kinds of headaches.

**Tension Headaches**

Tension headaches can be described as those that feel like a tight band across the head that can develop into more severe headaches with nausea, vomiting and photophobia. Diagnosis is made by presentation, family and personal history and exclusion of other etiologies such as neurological complaints, history of head trauma, recent stress or illness (Cunningham, 1999).

**Cluster Headaches**

Headaches that occur in close episodes then disappear for days to months are considered to be cluster headaches. They usually occur in men more than women, are unilateral, usually occur nocturnally, and cause lacrimation and nasal congestion. The patient usually must move around during the attack and often moans or yells, unlike those with migraine. Diagnosis is partially made when the patient finds relief with 100% oxygen administration and by exclusion
of other serious medical conditions including cerebral vascular accidents or aneurysms (Olesen et al., 1999).

**Diagnostic Cost, Sensitivity and Specificity**

Certain tests are routinely done to confirm a diagnosis of migraine. The approximate cost of a brain CT scan is $400-500, depending on region and if contrast is used in the test. The scan takes only minutes to complete and little preparation is needed. A CT scan is highly sensitive and specific to rule-out life threatening diseases and injuries that may occur in the central nervous system such as cerebral vascular accidents. Because of this, it should be considered first in radiological exams for patients who appear to present with critical findings (Olesen et al., 1999).

Magnetic resonance imaging (MRI) scan of the brain should be considered, if the patient presents with signs and symptoms of brainstem lesions, brainstem infarcts or multiple sclerosis. The cost is approximately $1000 (Jackson, 1998). MRI is indicated either when soft tissue injury is suspected or the results of a CT scan are inconclusive.

Lumbar puncture of the cerebral spinal fluid costs approximately $400. This test should be completed, if spinal meningitis, increased intracranial pressure or a cranial bleed is suspected. Sensitivity and specificity are high for bacterial and viral meningitis. However, results can take up to 48 hours, but the presence of red and white blood cells can be known within an hour (Uphold & Graham, 1998).

**Abortive Treatment of Acute Migraine Attacks**

Abortive therapy is therapy designed to arrest a migraine attack as early as possible. This specific treatment is given to those individuals who have been definitively diagnosed with migraine. A prior history should be completed before prescribing abortive therapy. Triptan
therapy is contraindicated in ischemic heart or cerebrovascular disease, uncontrolled hypertension and pregnancy. Aspirin and NSAIDS are contraindicated in individuals with bleeding disorders or known gastric ulcers (Olesen et al., 1999).

The choice of drugs may depend on the characteristics of the migraine attacks, not all attacks in the same patient may require the same drug. By contrast, MWA and MWOA are treated the same for abortive therapy. Mild, and sometimes moderate, attacks may be treated with aspirin, caffeine containing products, or nonsteroidal antiinflammatory drugs (NSAIDS), optimally combined with drugs that promote their absorption, such as metoclopramide (Olesen et al., 1999). When patients are uncertain, if a headache will develop into a migraine attack, they may choose to stage their treatment, first using less specific drugs such as aspirin, acetaminophen or NSAIDS. Specific anti-migraine drugs are more effective when there is an aura, when an impending migraine attack is recognized, or when the attack is already severe (Olesen et al., 1999). Please see Table 5 for considerations regarding treatment of acute migraine attacks.

When attacks are severe, the 5-hydroxytryptamine 1B and 1D (5-HT) receptor agonists: ergotamine (Ergomar), dihydroergotamine (D.H.E. 45), sumatriptan (Imitrex), zolmitriptan (Zolmig), naratriptan (Amerge), or rizatriptan (Maxalt) may be effective (Olesen et al., 1999). These drugs have been shown to bind to the trigeminal nucleus caudalis, as well as to its functional connections, reducing pain, nausea, and vomiting (Mathew, 2001). These drugs are thought to alleviate migraine by constricting large intracranial blood vessels and by blocking neurogenic inflammation. Activation of the 5-HT receptors inhibits the release of neuropeptides from the perivascular trigeminal sensory neurons, providing effective relief of migraine pain (Pascual, Falk, Docekal & Prusinski, 2001). All of the triptans are effective and are generally well tolerated, however, some patients will complain of feeling "drugged, hungover, and out-of-
it." Subtle differences exist between these agents in terms of pharmacokinetics, patient response and tolerability (Burkiewicz, Chan & Alldredge, 2000). Differences in triptan half-lives may prove to be important for those who are prone to headache recurrence within 24-hours of taking a medication. Naratriptan, which has a half-life of six to eight hours, has shown some potential advantages over shorter-acting triptans in terms of migraine recurrence (Sheftell, O’Quinn & Watson, 2000). The newest triptan, frovatriptan, has a half-life of 26 hours (Goldstein, Keywood & Hutchinson, 1999).

Triptans can be divided into classes based on the adverse effects they have on the body. DHE 45 is considered a first-generation triptan, or serotonin agonist, with little receptor selectivity. DHE exhibits pharmacological activity at several other receptor sites, which is responsible for the drug’s long list of side effects. The second-generation serotonin agonists, including Imitrex, Amerge, Maxalt, Ergomar, and Zolmig have greater receptor selectivity. However, these second-generation drugs still exhibit adverse effects that deter many migraineurs from using them (Beyzarov, 2000). For example, using Zolmig at 2.5 mg has been found to produce an overall satisfaction rate of 83.7%, compared to groups receiving acetaminophen, but at 5 mg the side effects, including dizziness, vertigo and nerve tingling, became pronounced and satisfaction dropped to 34.6% (Geraud, Compagnon & Rossi, 2002).

Research in Europe shows promise for those individuals who suffer from migraine but have been unable to use triptan therapy due to risks associated with cardiovascular ischemic events (Tonbridge, 2001). Eletriptan (Relpax), which has been approved in the UK and Europe, has been shown to be safe and effective in the treatment of migraine without serious side effects. This triptan is a newer generation with more neuronal selectivity. Eletriptan has not been shown to be adversely connected with the cardiovascular system. The study found a 59% positive
headache relief rate within two hours at 40 mg dosing. That percentage increased to 70% with 80 mg dosing (Tonbridge, 2001).

Other new triptans are being investigated, as well. For those individual who are at the risk of coronary artery disease, a large concern with triptan therapy, researchers are trying to develop triptans that will be selective for receptors within the brain. LY334370, a selective serotonin 5HT-1F receptor agonist is one of these medications. This drug has demonstrated efficacy of pain relief at 200 mg in 71% of patients LY334370 potentially blocks neurogenic inflammation and central in the trigeminal nucleus. LY334370 also does not demonstrate vasoconstriction in some vascular beds. In rabbits, LY334370 did not cause vasoconstriction of the saphenous vein, either alone or after modest pretreatment with prostaglandin 2-alpha. This drug demonstrated abortive therapy effectiveness, like many other triptans, for migraine relief with reduced potential for myocardial infarction, cerebral vascular accident or reduced circulation to the extremities (Goldstein, Roon, Offen & Ramadan, 2001).

The associated symptoms of the migraine, such as nausea and vomiting, may decrease absorption of oral medication due to gastric stasis. Using antiemetics and prokinetic agents may ameliorate the gastrointestinal manifestations and improve absorption (Olesen et al., 1999). These agents are dopamine receptor agonists that alleviate associated symptoms by acting centrally on the neuronal sites in the brain. During an attack the imbalance of neurotransmitters and vascular bed tone leads to an imbalances along dopamine and serotonin sites, causing nausea and vomiting (Olesen et al., 1999)

**Prophylactic Treatment**

Prophylactic treatment is considered in those patients who suffer from migraine attacks more than two to three times a month. The concept of prophylactic treatment is to prevent and/or
reduce the number of attacks a patient experiences. To initiate preventive pharmacotherapy for migraine attacks, a thorough evaluation must be completed. Prophylactic therapy should be considered in one or more of the following circumstances:

1. Incidence of attacks is more than two or three times per month.
2. Attacks are severe and impair normal activity.
3. The patient is psychologically unable to cope with the attack.
4. Optimal abortive therapies have failed or produced serious side effects.

The patient should keep a headache diary for at least one month so that the character and severity of the problem is documented. During prophylactic treatment, patients should keep a headache activity diary to help document the effects of treatment. Each medicine should be tried for approximately two to three months to judge effectiveness (Olesen et al., 1999). Please see Table 5 for considerations for prophylactic pharmacological therapy.

Preventive pharmacological therapy includes beta-blockers (propranolol/Imderal), calcium channel blockers (verapamil/Calan), and tricyclic antidepressants (amitriptyline/Elavil). Other therapies include NSAIDs (naproxyn/Naprosyn) and anticonvulsants (divalproex/Depakote) (Taylor, 2000).

Beta-blockers are usually the first line therapy for prophylaxis, unless contraindicated by bradycardia, asthma, or diabetes mellitus (Olesen et al., 1999). Propranolol (Inderal), generally well tolerated and effective, shows a 65% reduction rate of occurrences in migraine. Usually, a dosage of 80 mg/day is used and can be increased up to 240 mg/day (Diener, Kaube & Kimmroth, 1999).

Calcium channel blockers can also be used for prophylactic treatment. However, this classification of drugs is contraindicated in any patient with arrhythmias or cardiomyopathy.
Providing an approximate 60% effectiveness, tricyclic antidepressants such as amitriptyline (Elavil) can be considered effective prophylactic therapy (Moloney et al., 2000). Dosage is started at 30 mg at bedtime and can be increased to 100 mg. Clinical studies indicate that amitriptyline (Elavil) is the only antidepressant that has shown fairly consistent efficacy in the prevention of migraine (Scott Morey, 2000). However, this classification of antidepressants is contraindicated in pregnancy and frequently causes excessive drowsiness (Olesen et al., 1999).

Divalproex sodium, or Depakote, can be used to ameliorate migraine induced vomiting, photophobia, and phonophobia. However, therapeutic monitoring and adverse reactions to this drug make it a less desirable prophylactic treatment choice for migraine headaches (Taylor, 2000).

Finally, if by history, a patient’s migraine appears to be linked to the menstrual cycle, therapy with estrogen may be effective. Estrogen suppression during the late luteal phase, when estrogen is normally at its peak, thereby preventing a rapid estrogen decline, or estrogen supplementation during menses are possible therapeutic modalities (Olesen et al., 1999). Trials of estradiol, administered premenstrually as a gel or patch, suggest that a relatively high dose (1.5 mg per day of the gel form) may be effective in women, whose migraines are associated with their menstrual cycle (Morey, 2000). Triphasic oral birth control pills should be avoided due to varying estrogen levels throughout the cycle and tolerance to therapy may be lower (Diamond, 2000). Patients with cardiovascular risk, who smoke, or who are over the age of 35
should not be put on this type of therapy due to increased risk of stroke and thromboembolism (Olesen et al., 1999).

**Alternative Therapies**

Alternative therapies can be used as well as pharmacological interventions for the treatment of migraine. The herbal preparation feverfew has been shown to reduce photophobia, pain intensity, nausea, vomiting, and phonophobia (Morey, 2000). However, with many herbal preparations, there is no standardization of the preparation or active ingredients. This makes it difficult to know to what degree these herbal supplements are therapeutic (Morey, 2000). According to International Headache Society guidelines, relaxation training, thermal biofeedback combined with relaxation training, electromyographic (EMG) biofeedback and cognitive-behavioral therapy are somewhat effective in preventing migraine. Studies find that when these type of therapies are used in conjunction with pharmacological therapy patients have a lower rate of migraine recurrence and higher pain relief rate (Scott Morey, 2000).

**The Role of Education**

Primary care and obstetrics offices are excellent places to begin to screen patients for migraine attacks in order to appropriately identify migraineurs. Research has found that many migraineurs go undiagnosed for many years until the pain and frequency of attacks becomes so great they are forced to seek medical care. Many researchers feel migraines may begin in the early teens and become progressively worse with each decade, making primary care offices good places to screen young adults. In addition, with 18% of migraineurs being women obstetric/gynecology offices are also good screening locations (Mathew, 2001). Using key questions in all screening exams helps to identify those individuals who may be suffering from migraine. By identifying those individuals with migraine, practitioners can improve therapy,
give effective education and help identify triggers that may cause migraine. It is important to develop a lasting clinician-patient relationship with migraine patients. Migraineurs may have experienced multiple clinical visits with many providers. Mistreatment and underdiagnosis can lead to long-term dependence on opiate or barbiturate medications, gastrointestinal problems, and kidney problems related to chronic NSAID use. Taking time with patients, understanding their treatment goals, and allowing them to become partners in their own care will help the practitioner develop a valuable therapeutic relationship (Fox, Sharfman, Jones & Fitzgerald, 2002). In addition, the practitioner should identify treatment goals at each visit. These should include effective abortive therapy, identifying possible triggers, how to avoid these triggers, and appropriate steps for the patient to take if an attack occurs. The practitioner should also help the patient design a diary, noting dates, times and duration of attacks. This diary should include alleviating and aggravating factors, if abortive therapy was helpful and dosages and number of medications used to treat an attack. The practitioner should review this diary periodically with the patient to identify if treatment strategies are effective or if different therapy or further education needs to be completed. Migraine patients should be followed approximately every three months until patient and practitioner goals are met. The patient may be followed every six months or yearly if patient satisfaction and treatment goals are met. Please see Table 6 for outline of patient education information.

Conclusion

Migraine headache is a complex disease process that affect millions of people a year. Genetic predisposition and subsequent abnormalities in the central nervous system result in neurochemical imbalance and subsequent vasodilation. For those individuals who suffer from migraine that are the result of other pathophysiological conditions therapies are available to treat
their underlying condition. With future research into the causes of migraine, new and innovative therapies may become available. Until that time, specific therapies such as triptans are available for abortive therapy. Prophylactic therapy remains a modality for those who appear to have progressed into a chronic disease state. Using appropriate diagnostic tools and therapeutic modalities a migraineur can understand and treat their symptoms effectively. Quality-of-life can be greatly improved in individual patients with effective individualized treatment plans. The nurse practitioner can be instrumental in helping patients understand, identify and comprehend the pathophysiology and treatment options of migraine attacks. Practitioners can educate, provide and aid patients in developing treatment plans tailored individually for their lives, activities and goals of therapy.
References


Table 1
INTERNATIONAL HEADACHE SOCIETY CRITERIA FOR MIGRAINE

**Migraine Without Aura**

- At least 5 attacks, lasting 4-72 hours, at least two from Group A, and one from Group B
  - Group A:
    1. Pain is unilateral
    2. Pain is pulsatile or throbbing
    3. Pain is aggravated by normal activity (such as climbing stairs, bending over)
    4. Moderate to severe pain that limits normal activity
  - Group B:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia

**Migraine With Aura**

- At least 2 attacks, gradual onset of reversible focal neurological symptoms, headache lasting 4-72 hours, at least 3 from Group A and one from Group B.
  - Group A:
    1. One or more fully reversible neurological symptoms (such as scotomas, parasthesias, or weakness)
    2. No aura symptom lasts longer than 60 minutes
       Headache follows aura free period of not more than 60 minutes.
  - Group B:
    1. History and exam do not suggest other disorder.
    2. Other disorders are ruled out by thorough investigation.
    3. Other disorders are present, but not temporally related to the migraine.

(Olesen et al., 1999) (Morey, 2000)
Table 2

COMMON MIGRAINE TRIGGERS/MECHANISMS

<table>
<thead>
<tr>
<th>Physical</th>
<th>Menstruation, Exercise, Altered Sleep Pattern, Irregular Meals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>Red Wine, Aged Cheese, Bacon, Chocolate, Liver, Alcohol, Aspartame, Monosodium Glutamate, Caffeine</td>
</tr>
<tr>
<td>Emotional</td>
<td>Anxiety, Stress, Excitement, Anger Depression, Post-stress (Weekend Vacation)</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>Chronic Pain Medication Use, Cocaine Use and Withdrawl, Tobacco Use, Nitroglycerin, Estrogen, Histamine, Ranitidine</td>
</tr>
<tr>
<td>Sleep Related</td>
<td>Lack of Sleep, Excessive Sleep</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Head Trauma, Physical exertion, Fatigue, Neck and Back Spasms</td>
</tr>
</tbody>
</table>

(Olesen et al., 1999) (Morey, 2000)
### Table 3

**SYMPTOMS AND SIGNS DURING PHASES OF A MIGRAINE ATTACK**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Appetite</td>
<td>Cravings</td>
<td>Anorexia/Vomiting</td>
<td>Limited Food Intake</td>
<td>Appetite</td>
</tr>
<tr>
<td>Awake/Sleep</td>
<td>Tired/yawning</td>
<td>Photophobia</td>
<td>Tired</td>
<td>Awake/Sleep</td>
</tr>
<tr>
<td>Light Tolerance</td>
<td>Heightened Perception</td>
<td>Phonophobia</td>
<td>Feeling High or Low</td>
<td>Light Tolerance</td>
</tr>
<tr>
<td>Noise</td>
<td>Fluid Retention</td>
<td>Osmophobia</td>
<td>Diuresis</td>
<td>Noise</td>
</tr>
<tr>
<td>Smell</td>
<td></td>
<td>Deep Sleep</td>
<td></td>
<td>Smell</td>
</tr>
<tr>
<td>Fluid Balance</td>
<td></td>
<td></td>
<td></td>
<td>Fluid Balance</td>
</tr>
</tbody>
</table>

(Olesen et al., 1999) (Morey, 2000)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular Accident</td>
<td>Sudden onset of focal neurological changes; vascular hemorrhage or ischemia; evaluate with H/P and CT/MRI.</td>
</tr>
<tr>
<td>Cluster Headache</td>
<td>Vascular in nature with genetic predisposition. Relieved with 100% O2; evaluate with H/P, may do CT if indicated.</td>
</tr>
<tr>
<td>Intracranial Abscess</td>
<td>Focal neurological changes accompanied by fever, malaise and sepsis. Evaluate with H/P and CT with and without contrast.</td>
</tr>
<tr>
<td>Intracranial Tumor</td>
<td>Onset of headache that gradually becomes worse to severe. Followed by focal neurological changes, changes in LOC. Evaluate with H/P, CT scan and MRI.</td>
</tr>
<tr>
<td>Hypertension Headache</td>
<td>Caused by elevated blood pressure, results in frontal head pain. Evaluate based on H/P, physical Examination. Use exercise, pt. Education, blood pressure medication, and relaxation to relieve pain.</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Evaluate for nuchal ridigity, severe headache, fever, malaise, and changes in LOC. Results from infection of the CNS causing inflammation of the meninges. Evaluate with LP, CT if decreasing LOC and CBC with differential.</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Caused by allergies, viruses and bacteria that invade the sinuses of the facial region causing pain, pressure and congestion. Evaluate with H/P, treatment modalities, if it is acute or chronic, and CT, if unresolved after multiple treatments.</td>
</tr>
<tr>
<td>Subarachnoid Hemorrhage</td>
<td>Vascular hemorrhage of the brain. May have sudden onset with decreased LOC, vomiting and may be trauma related. Evaluate with H/P and CT/MRI.</td>
</tr>
</tbody>
</table>
Tension Headache

Vascular headache caused by muscular tension and stress. Evaluate patient with H/P, use muscle relaxants/relaxation, mild analgesics and NSAIDS.

(Olesen et al., 1999) (Fox & Davis, 1998)
## Table 5

**CONSIDERATIONS IN PHARMACOLOGIC TREATMENT**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is it a migraine?</td>
<td>Have patient keep a diary of headache for at least one month. Observe for drug misuse and over use.</td>
</tr>
<tr>
<td>2. What Drug?</td>
<td>Use Aspirin or a NSAID.</td>
</tr>
<tr>
<td>Mild Attack?</td>
<td>Use specific treatment modality, including triptans.</td>
</tr>
<tr>
<td>Severe Attack?</td>
<td>If the aura is less than 30 minutes an ergotamine can be used. Sumatriptan is not effective given in the aura phase.</td>
</tr>
<tr>
<td>Aura Association?</td>
<td>Nausea and vomiting can be treated with a prokinetic or an antiemetic, such as metoclopramide.</td>
</tr>
<tr>
<td>3. Associated Symptoms</td>
<td>Examine if drug therapy was used appropriately and at therapeutic levels.</td>
</tr>
<tr>
<td>4. Previous drug use?</td>
<td>Know the patient's cardiovascular history.</td>
</tr>
<tr>
<td>5. Contraindications?</td>
<td>Ergotamine and triptans are related to ischemic vascular events. Always know pregnancy status.</td>
</tr>
<tr>
<td>6. Route of administration?</td>
<td>Vomiting may prohibit p.o. intake, an intramuscular, subcutaneous, or rectal route may need to be used.</td>
</tr>
<tr>
<td>7. Prophylactic Treatment?</td>
<td>Must have had more than two attacks per month, that cannot be treated effectively with abortive therapy.</td>
</tr>
<tr>
<td>Choice of drugs?</td>
<td>Beta Blockers, Calcium Channel Blockers, tricyclic antidepressants, anticonvulsants, and SSRIs. (Know contraindications for all of these classes).</td>
</tr>
<tr>
<td>Dosage?</td>
<td>There is no &quot;standard&quot; dosage in migraine patients. Tailor the drug to fit the individual.</td>
</tr>
<tr>
<td>Side Effects?</td>
<td>Inform patients of potential mild to severe side effects of all prophylactic treatment options.</td>
</tr>
</tbody>
</table>

(Olesen et al., 1999) (Fox & Davis, 1998)
<table>
<thead>
<tr>
<th>PATIENT EDUCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Headache Diary</strong></td>
</tr>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td><strong>Computed Tomography</strong></td>
</tr>
<tr>
<td><strong>Lumbar Puncture</strong></td>
</tr>
<tr>
<td><strong>Magnetic Resonance Imaging</strong></td>
</tr>
</tbody>
</table>

(Olesen et al., 1999) (Morey, 2000)
Figure 1

PATHOPHYSIOLOGY OF MIGRAINE WITH AURA

Genetic Predisposition
(19p13, ACE-D allele)

Channelopathy

Central Neuronal Hyperexcitability

Spreading Depression

Brainstem Activation

Trigeminal Vascular Activation

Migraine Pain

Ischemia and hypoperfusion

Chronic neuronal dysfunction

(Mathew, 2001)
PATHOPHYSIOLOGY OF MIGRAINE WITHOUT AURA

Activation of Rostral Brainstem

→

Bilateral Activation of Regions (intracranial and extracranial blood vessels)

→

Activation of the cingulate cortices and cerebellar cortices (bilaterally)

→

Activation of the Thalamus

→

Migraine Pain

→

Ischemia and hypoperfusion

→

Chronic neuronal dysfunction

(Mathew, 2001)
Figure 3

ALGORITHM OF HEADACHE DIAGNOSIS

Headache

H & P, Family History, Medical History

Headache history with no change

H/P normal

Keep headache diary, analgesics

Monitor

No Headache history

LOC change, trauma or acute onset

Febrile, Nuchal Rigidity

CT Normal

LP, CBC

Normal

Monitor

Analgesics/monitor

CT Abnormal (Neurological Referral)

CT Normal

Antibiotics, steroids

Supportive care,
Neurological & Infectious Disease Referral

CBC = Complete Blood Count

(Ølesen et al., 1999) (Fox & Davis, 1998)